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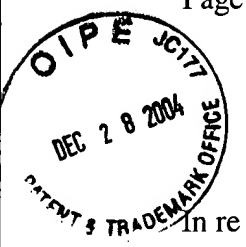

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re PATENT APPLICATION of	Confirmation No.: 8046
MOODY et al	Group Art Unit: 1654
Appln. No.: 09/457,765	Examiner: M. Meller
Filed: December 10, 1999	Attorney Docket: 121640-40265189

Title: PROCESS FOR THE PREPARATION OF AMPICILLIN

* * * * * * * * * *

December 28, 2004

APPELLANTS' BRIEF UNDER 37 C.F.R. § 41.37

Mail Stop POBA
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22131-1450

Sir:

Further to the Notice of Appeal under 37 C.F.R. 43.31 filed October 28, 2004, Moody et al, Appellants herein, appeal from the decision of the Primary Examiner, dated July 28, 2004, finally rejecting claims 1-4, 6-8, 11 and 14-16, all of the claims pending in this application. This appeal is taken with respect to all of the finally rejected claims.

The $500.00 fee required by 37 C.F.R. 41.20(b)(2) is authorized to be charged to Deposit Account 503-121; please reference Attorney Docket: 121640-40265189. Please charge any additional fees associated with the submission of this paper to Deposit Account Number 503-121. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

(i) ***Real party in interest.***

The assignee of the subject application and the real party in interest is DSM IP Assets, B.V., Heerlen, The Netherlands.

(ii) ***Related appeals and interferences.***

There are no related appeals or interferences.

(iii) ***Status of claims.***

Claims 1-4, 6, 7 and 14-17 are pending and are finally rejected. Claims 1 and 17 are the only independent claims.

Claims 5 and 8-13 are cancelled.

This appeal is taken with respect to all of the finally rejected claims 1-4, 6-7, and 14-17.

(iv) ***Status of amendments.***

No amendments were filed subsequent to the date of the Final Rejection.

(v) ***Summary of claimed subject matter.***

The claimed subject matter, as set forth in independent claim 1, relates to a process for the preparation of ampicillin, a β-lactam derivative. More particularly, the claimed subject matter relates to the enzymatic acylation of 6-aminopenicillanic acid (hereafter, "6-APA"), a compound having a β-lactam nucleus, in the presence of an acylation agent, such as a glycine derivative (page 1, lines 8-17).

As set forth in claim 1, the process is carried out under the following conditions:

i) the total combined concentration of 6-APA and ampicillin in the reaction mixture is greater than 250 mM, preferably, greater than 300 mM (page 1, lines 12-14; page 3, line 26 to page 4, line 2, graph 2);

ii) the concentration of dissolved 6-APA in the reaction mixture is lower than 300 mM (page 1, lines 14-15; page 4, lines 3-5, graph 2); and

iii) the molar ratio of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than 2.5 (page 1, lines 15-17; page 3, lines 15-20, graph 2).

Furthermore, the condition ii) may be achieved by initially charging only part of the total quantity of (*i.e.*, metering in partially) the 6-APA and/or the phenylglycine derivative in the course of the acylation reaction (page 4, lines 13-18; page 5, lines 1-6).

Thus, according to the involved embodiments of the present invention, ampicillin is prepared by enzymatically acylating 6-APA with a phenylglycine derivative in a reaction mixture which include generally low concentrations of dissolved 6-APA and that achieve a higher conversion of 6-APA can be achieved than would be possible if the concentration of dissolved 6-APA were made as high as the prior art suggests (page 2, lines 23-28).

Suitable types and classes of enzymes which are useful in embodiments of the present invention are exemplified on page 6, lines 3-21.

The embodiment set forth in independent claim 17 is substantially similar to the embodiment set forth in claim 1. According to claim 17, the acylation reaction between a quantity of 6-APA with a quantity of phenylglycine derivative and an enzyme is carried out in an aqueous reaction medium (see, *e.g.*, page 7, lines 11-20). As set forth in claim 17, the process includes a step of initially introducing a part of the quantity of 6-APA and/or a part of the quantity of phenylglycine derivative into the reaction medium under conditions allowing ampicillin to be formed by the acylation reaction. Thereafter, the process includes a step of adding the rest of the quantity of 6-APA and/or phenylgycine derivative, under conditions whereby ampicillin will continue to be formed by the acylation reaction (see, *e.g.*, page 4, lines 3-5 and 13-18; page 5, lines 7-11).

According to claim 17, as in the embodiment of claim 1, the concentration of dissolved 6-APA in the reaction mixture is, throughout the acylation reaction, lower than 300 mM (page 4,

lines 3-5); the total combined concentrations in the reaction mixture of 6-APA and formed ampicillin is greater than 250 mM (page 3, line 26 to page 4, line 1); and the molar ratio of the quantity of phenylglycine derivative to the quantity of 6-APA is less than 2.5 (page 3, lines 15-20).

By operating the enzymatic acylation reaction under the conditions specified in the rejected claims, the conversion of 6-APA to ampicillin is higher than would be achieved by operating at a higher concentration of the dissolved 6-APA (page 2, lines 23-28). Embodiments of the invention provide the further advantage that at the relatively low concentration of dissolved 6-APA, the stirrability of the reaction mixture is improved (page 2, line 29 to page 3, line 2).

It has been shown by the examples in WO-A-92/01061 that high conversions of the acylation agent to β-lactam nucleus are achieved when the molar ratio of acylation agent to β-lactam nucleus, is high and, conversely, the conversion is lowered when this molar ratio is lowered. However, Appellants recognized that offsetting the advantage of such high molar ratio is (1) the loss of the acylating agent due to hydrolysis (page 1, lines 18-31) and (2) the difficulty in separating the product ampicillin from a large quantity of the acylating agent (phenylglycine) (page 1, line 31 to page 2, line 5).

(vi) ***Grounds of rejection to be reviewed on appeal***

The grounds of rejection to be reviewed include the following:

(1) Whether the Examiner has erred in rejecting claims 1-4, 6, 7, and 14-17, under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement; and, more specifically, whether the Examiner has erred by

(a) concluding that claims 14-16 are not supported by the specification because allegedly there is no support for "charging a portion of the total amount of 6-APA to the reaction mixture at the beginning of the reaction such portion providing a concentration of dissolved 6-

APA less than 300 mM and introducing the remainder of the total amount during the remainder of the acylation reaction";

(b) concluding that claim 17 is not enabled for "a part" in the phrase "a part of said quantity of the 6-APA "and for when is the ampicillin to be formed by the acylation reaction is done."

(2) Whether the Examiner has erred by rejecting claims 1-4, 6, 7 and 14-17, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention; and, more specifically, whether the Examiner has erred by concluding that,

(a) claim 1 is not clear in view of the absence of antecedent basis for the language "maintaining the total concentration in the reaction mixture" and the "acylation reaction";

(b) claim 1 does not make clear how one can measure the "total concentration" of 6-APA and ampicillin in the reaction mixture;

(c) step iii) in claim 1 suffers from lack of antecedent basis;

(d) claim 1 is confusing at what point in the reaction the acylation occurs;

(e) claim 1 is indefinite for not reciting definite steps in chronological order;

(f) claim 1 is indefinite because the metering step is a definite step not a "maintenance" step;

(g) claims 2 and 4 are indefinite because it would be clearer if they stated that they occurred in step i) and step ii), respectively,

(h) claims 14-16 are indefinite (confusing) since it is not clear what "portion" is;

(i) claims 14-16 are indefinite (confusing) in view of the term "charged";

(j) claims 14-16 are indefinite with respect to "portion";

(k) claim 17 is indefinite for introducing the phrase "a part of said quantity of 6-APA"; and

(l) claim 17 is indefinite with respect to when the ampicillin to be formed by the acylation reaction is done and how one would know that this has been achieved.

(3) Whether the Examiner has erred in rejecting claims 1-4, 6, 7, and 14-17, under 35 U.S.C. § 103(a) as being unpatentable over WO 92/01061 taken with WO 95/03420.

(vii) ***Arguments***

(1) Rejections under 35 U.S.C. § 112, first paragraph

A. Claims 1-4, 6, 7

With respect to claims 1-4, 6 and 7, the rejection should not be sustained because no reason for the rejection of these claims is included in the Final Rejection.

In the previous action, dated November 19, 2003, a separate ground for rejection of claim 1, under 35 U.S.C. § 112, first paragraph was stated . That ground of rejection (presumably because the basis thereof was no longer pertinent) was not repeated in the Final Rejection.

Thus, it is believed that the rejection under the first paragraph of Section 112, which includes claims 1-4, 6 and 7, was unintended but, in any event, absent any specific reason in support thereof, the rejection, as applied to these claims, should not be sustained.

According to 37 C.F.R. §1.104(a)(2) the applicant will be notified of the examiner's action and,

> "[t]he reasons for any adverse action or any objection or requirement will be stated in an Office action and such information ... will be given as may be useful in aiding the applicant, ... to judge the propriety of continuing the prosecution."

Here, the examiner has failed to state any reasons for the adverse action.

Furthermore, in discussing final rejections or actions, Rule 113(b) [37 C.F.R. § 1.113(b)] provides that an examiner, in making a final rejection, "shall repeat or state all grounds of rejection then considered applicable to the claims in the application, clearly stating the reasons in support thereof."

This has not been done.

Therefore, the Honorable Board of Patent Appeals and Interferences (hereafter, "Board") should reverse the rejection of claims 1-4, 6 and 7, under 35 U.S.C. § 112, first paragraph.

B. Claim 14-16

The specification provides a clear written description supporting the claim language, "charging a portion of the total amount of 6-APA to the reaction mixture at the beginning of the reaction such portion providing a concentration of dissolved 6-APA less than 300 mM and introducing the remainder of the total amount during the remainder of the acylation reaction." The written description requirement is satisfied by at least the language in the specification at page 4, lines 15-18, which explains that, "[o]ne possibility of keeping the concentration of dissolved 6-APA low is to initially charge only part of the total quantity of 6-APA and add the rest during the reaction."

It is not relevant that the language in the specification and the language in the claims do not match *ipsis verbis*, it being sufficient that the specification clearly conveys to the practitioner of ordinary skill in the art that Appellant was in possession of the subject matter now being claimed. It is the "possession" of the claimed subject matter, not the presence or absence of literal supporting language. Thus, the Federal Circuit has approved the following test stated by the Board in *In re Kaslow*, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983):

> "The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language.

In re Edwards, [568] F.2d 1349, 196 USPQ 465 (CCPA 1978); *In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979)."

The disclosure of the specification clearly conveys that Appellant wise in possession of the claimed invention wherein a part of the total amount (or "a portion") of 6-APA is charged to the reaction mixture at the beginning of the reaction (or "initially") to provide a concentration of dissolved 6-APA less than 300 mM (*i.e.*, to keep the concentration of dissolved 6-APA low) and introducing the remainder of the total amount during the acylation reaction (*i.e.*, "add the rest during the reaction").

Since there is clear and unequivocal support in the specification for the language of claim 14 (and no separate issue is raised for the language of claims 15 and 16) there is no failure to comply with the "written description" requirement of the first paragraph of 35 U.S.C. § 112.

Accordingly, the Honorable Board should not sustain this ground of rejection as applied to claims 14-16 and reversal of this rejection is respectfully requested.

C. Claim 17

The rejection refers to the language requiring introducing "a part of said quantity of the 6-APA" but questions the enablement for "a part;" asking how much is "a part"?

It is not clear how this rejection applies to the stated basis of the rejection, namely, that the claims fail to comply with the written description requirement.

To the extent that the rejection is, in fact, one for apparent lack of written description, it is again explained that the specification clearly conveys that Appellant was in possession of the subject matter now being claimed. The specification, at page 4, lines 15-18, explains that, "[o]ne

possibility of keeping the concentration of dissolved 6-APA low is to initially charge only part of the total quantity of 6-APA and add the rest during the reaction."

Accordingly, the rejection of claim 17, under the first paragraph of 35 U.S.C. § 112, should not be sustained by the Honorable Board.

If, however, the examiner intended to make a non-enablement rejection, it is respectfully submitted that this was not done and, therefore, the rejection should not be sustained.

Nevertheless, there is no objective basis for doubting the enablement of the specification or for putting a specific numerical requirement on "a part." The specification, and the claim language, both clearly explain that the amount of the 6-APA that is initially introduced to the reaction mixture is such that the concentration of dissolved 6-APA in the reaction mixture is, throughout the acylation reaction, lower than 300 mM. The examiner has not questioned that the ordinarily skilled practitioner would have known how this may be accomplished, nor does the Examiner question that the specification would have enabled the ordinarily skilled practitioner to determine an amount of the 6-APA which yields a concentration of dissolved 6-APA of lower than 300 mM. Indeed, the specification, beginning on page 4, line 13, describes several ways that the concentration of dissolved 6-APA may be kept low.

Therefore, there is objective enablement for this requirement of the rejected claim 17.

Similarly, with regard to the inquiry "when is the ampicillin to be formed by the acylation reaction done," and the suggestion that there is no enablement for this in the specification, it is again respectfully submitted that "enablement" is not a basis for a lack of written description rejection but, in any case, the specification is fully enabling for the claimed invention.

Initially, it is submitted that the claim language does not require the acylation reaction to "be done." Rather, the practitioner may stop the reaction at any convenient time. The language in claim 17 does, however, set forth the concentration of dissolved 6-APA in the reaction mixture (throughout the reaction), and specify the total combined concentrations in the reaction mixture of 6-APA and formed ampicillin, as well as a molar ratio of the quantity of

phenylglycine to the quantity of 6-APA. These requirements do not specify an "end" to the acylation reaction.

Thus, one skilled in the art would understand that the reaction may be, for example, a batch reaction or a continuous reaction, and both types of reactions are described in the specification:

> "The enzymatic acylation reaction is preferably carried out as a batch process. If desired it is also possible to carry out the reaction continuously, with the concentration of dissolved 6-APA being controlled in line." (page 3, lines 21-25)

On the other hand, the specification also explains that the reaction may be almost completely stopped when near to maximum conversion has been achieved. In this case, the conversion would be understood as referring to the conversion of 6-APA to ampicillin (see, *e.g.*, the specification at page 3, lines 3-5). The specification also illustrates representative embodiments as to how this stoppage may be accomplished (see, *e.g.*, page 7, lines 23-29). The Example and Comparative Example on pages 10-11 also provide additional guidance on how the process according to embodiments of the present invention can be carried out.

Therefore, claim 17 should be found to be in compliance with all requirements of 35 U.S.C. 112, first paragraph.

Accordingly, whether the rejection under the first paragraph of 35 U.S.C. § 112, was intended to be for lack of written description or enablement, the rejection should not be sustained by the Honorable Board.

Therefore, reversal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

(2) Rejections under 35 U.S.C. § 112, second paragraph

A. Claim 1

(a) It is stated that there is no antecedent basis for "maintaining the total concentration in the reaction mixture." However, the term "maintaining" does not appear in Claim 1.

Accordingly, this basis for rejection should not be sustained.

It is also stated that the phrase "the acylation reaction" does not have antecedent basis in the claims. However, claim 1 clearly refers to the step of "acylating 6-aminopenicillanic acid (6-APA) with a phenylglycine derivative and an enzyme to form a reaction mixture." (Emphasis added.) It is, therefore, apparent that there is antecedent basis for "the acylation reaction."

Accordingly, this basis for rejection should not be sustained.

(b) It is further alleged that the claim language "the total concentration" of 6-APA and ampicillin is unclear because the whole purpose is to produce ampicillin.

The language in claim 1 is not unclear. Since 6-APA is introduced as a reactant during the course of the acylation reaction, and since ampicillin is produced as a result of the acylation reaction, there will be, "substantially throughout the reaction" some amount of 6-APA and ampicillin. All that is stated in the objected to language is that the "total concentration in the reaction mixture of 6-APA and ampicillin combined" be greater than 250 mM.

The practitioner of ordinary skill in the art would not have any difficulty in understanding the meaning and scope of this claim.

For completeness, it is also observed that the rejection suggests that there is no description in the specification for the total concentration of 6-APA and ampicillin. With due respect, attention is directed to the paragraph bridging pages 3 and 4 of the specification, which explicitly states that "the total concentration of 6-APA plus ampicillin (in dissolved and in undissolved form) in the reaction mixture is made higher than 250mM . . ." Moreover, the graphs 1 and 2 show the concentration of the total amount of 6-APA and the total amount of ampicillin, each as a function of time, such that the total combined concentrations, at any time during the course of the acylation reaction, can be readily determined.

Accordingly, this basis for rejection should not be sustained.

(c) It is next suggested that the phrase "total quantity of phenylglycine derivative" in "step iii)" has a problem of antecedent basis.

Initially, it is submitted that iii) is not a "step" but rather a "condition" under which the acylation reaction is carried out.

In any case, since claim 1 explicitly recites acylating 6-APA with a phenylglycine derivative, and further permits metering in partially the phenylglycine derivative, there will necessarily be a "total quantity" of phenylglycine derivative, from which the molar ratio in iii) can be determined.

Therefore, claim 1 does not suffer from lack of antecedent basis or indefiniteness because of the reference in iii) to "the total quantity of phenylglycine derivative."

Accordingly, this basis for rejection should not be sustained.

(d) It is asserted that the claim language is confusing with regard to the point in the reaction that the acylation occurs, presumably with reference to ii).

Although the basis for this confusion and rejection is not understood, it need merely be noted that the practitioner would understand that the acylation reaction occurs over a period of time, whether the reaction is carried out as a batch reaction or as a continuous or semi-continuous reaction. The condition of step ii) refers to the "course of the acylation reaction" and the practitioner of ordinary skill would understand this phrase to mean that the reaction is not completed instantaneously but occurs over a period of time.

(e) The examiner has also suggested that "Appellant needs to present claim 1 with definite steps in chronological order." Appellant respectfully disagrees that there is any such requirement. The language of claims 1-4 is not somehow made indefinite or unclear by requiring that the process for the preparation of ampicillin (which involves acylating 6-APA with a phenylglycine derivative and an enzyme) is carried out i) while the total concentration of 6-APA

and ampicillin combined is greater than a specified amount; ii) while metering in partially the 6-APA and/or phenylglycine derivative in the course of the acylation reaction to maintain a specified concentration of dissolved 6-APA, and iii) while the molar ratio of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than a specified amount. The claim language is not indefinite but clearly conveys that the conditions or steps i), ii) and iii) take place during the course of the acylation reaction, and further particularizes the acylation reaction as well as distinguishes the reaction from the prior art.

(f) Finally, it is urged that claim 1 is indefinite because the "metering step is a definite step not a 'maintenance' step."

Claim 1, under appeal, as presented in the Amendment dated April 16, 2004, does not include the word "maintenance" or otherwise suggest that the metering step is a "maintenance" step. What is clearly and definitely stated, however, is that metering in partially the 6-APA and/or the phenylglycine derivative in the course of the acylation reaction is a positive manipulative step such that the concentration of dissolved 6-APA is lower than 300 mM throughout the reaction.

Therefore, claim 1 is not indefinite for the reason of the language of "metering in partially ... to thereby maintain" a concentration of dissolved 6-APA.

Accordingly, all of the bases for rejection of claim 1 under 35 U.S.C. § 112, second paragraph, are not well taken and the rejection should not be sustained by the Honorable Board.

Therefore, the rejection of claim 1 as indefinite should be reversed.

B. Claims 2 and 4

It is next suggested that claims 2 and 4, would be clearer if it were stated that the conditions recited in these claims occurred in step i) and step ii) (sic, iii)), respectively.

Although Appellants do not understand this comment to be a "rejection" but rather a mere "suggestion" nevertheless it is respectfully submitted that claims 2 and 4 are not indefinite

for failing to associate the more specific limitation of claim 2 with the condition i) [noting that only the condition i) refers to the "total concentration of the 6-APA and ampicillin present in the reaction mixture"] or for failing to associate the more specific limitation of claim 4 with the condition iii) [noting that only the condition iii) refers to "the molar ratio of the total quantity of 6-APA"].

Accordingly, the rejection of claim 2 as indefinite should not be sustained and this ground for rejection should be reversed.

C. Claims 14-16

Appellants respectfully disagree with the Examiner's assertion that these claims are "very confusing to the point of being meaningless." None of the specific alleged defects pointed to in the rejection warrant such a conclusion.

Neither the terms "portion," or "charging" are confusing or render these claims indefinite.

Claim 14 recites a step of "charging a portion of the total amount of 6-APA to the reaction mixture at the beginning of the reaction." Moreover, it is further explained that the "portion" provides a concentration of dissolved 6-APA less than 300 mM.

There is nothing in the specification which would suggest that these terms have anything other than their normal meanings. In this case, "charging" means simply feeding or introducing or supplying.

Thus, "charging a portion" would be understood by a person of ordinary skill in the art to mean that an amount, less than the total amount, i.e., a "portion," is furnished to the reaction mixture.

The claim may be somewhat broad for not reciting the particular portion (other than that the portion is such that the concentration of dissolved 6-APA is less than 300 mM), but breadth does not equate with indefiniteness, *see, e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (explaining that

definiteness in claims and enabling support are distinct requirements); *Process Control Corp. v. Hydreclaim Corp.* 190 F.3d 1350, 22 USPQ2d 1029 (Fed. Cir. 1999).

Therefore, since the language of claim 14 would be readily understood by the person of ordinary skill in the art so that the metes and bounds of the claimed invention may be readily ascertained, the rejection of claims 14-16 as indefinite should not be sustained.

D. Claim 17

Similarly, the language found indefinite in claim 17, namely, "a part of said quantity of the 6-APA" clearly refers to the quantity of the 6-APA (and/or the quantity of phenylglycine derivative). Thus, the practitioner reading claim 17 would understand that less than the entire amount of 6-APA (and/or phenylglycine derivative) is introduced into the reaction medium. Again, that the specific amount is not specified does not render the claim indefinite since the practitioner would immediately and unquestionably know whether the amount added is less than the total quantity (i.e., a "part") to be added (the following step in claim 17 calls for "thereafter adding the rest of the quantity of 6-APA...").

Moreover, as previously explained, in the case of a continuous reaction, the formation of ampicillin by the acylation reaction may not be "done" until it is decided to terminate the reaction for whatever reason. Nevertheless, the practitioner, following the disclosure and based on ordinary skill in the art, would know when the reaction was "done" as in a batch reaction, for example. Indeed, according to an embodiment of the invention described in the specification at page 7, lines 21-23, the "reaction is preferably almost completely stopped when near to a maximum conversion has been achieved." The specification then continues to explain how this may be accomplished, and the examples further demonstrate the course of the reaction.

All that is required to satisfy the definiteness requirement of the second paragraph of Section 112, is that the claims "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits." *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

If those skilled in the art would understand what is claimed when the claim is read in light of the specification, a claim is not invalid for indefiniteness, *Morton International, Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (Fed. Cir. 1993), *on remand from*, 508 U.S. 83, 26 USPQ2d 1721 (1993); *Process Control Corp. v. Hydreclaim Corp., supra.*

Since the language of claim 17 reasonably conveys the subject matter which Appellants regard as the invention and allow the practitioner to understand the bounds of the claim, the rejection of claim 17 as indefinite should not be sustained.

For all of the foregoing reasons the Honorable Board of Patent Appeals and Interferences should reverse the decision of the Primary Examiner rejecting claims 1-4, 6, 7 and 14-17, under 35 U.S.C. § 112, first and second paragraphs.

(3) Rejection under 35 U.S.C. § 103(a)

A. Claims 1-4, 6, 7, 14-17

The rejection of claims 1-4, 6, 7 and 14-17 under 35 U.S.C. § 103(a) as being unpatentable over WO 92/01061 (WO '061) taken with WO 95/03420 (WO '420), should also not be sustained and should be reversed.

The claims on appeal are patentable, at least for the reason that the cited prior art does not disclose or suggest metering either or both of the 6-APA or phenylglycine derivative to the reaction mixture. The practitioner of ordinary skill would not have been motivated to carry out the enzymatic acylation reaction under these conditions because the cited references do not suggest that metering would be effective to maintain the concentration of 6-APA at lower than 300 mM, or that maintaining the concentration of 6-APA in the reaction media at any particular concentration, including a concentration lower than 300 mM or 250 mM, would have a beneficial effect on the outcome of the reaction.

It is, however, the Examiner's position that

> "[t]o add slowly and in a meticulous manner as in metering is well known in the art and is fully contemplated by the references. One of ordinary skill in the art reading the references would have fully realized that adding in the ingredients slowly in a meticulous fashion would work well. It is simply the choice of the artisan in an effort to optimize the results to add the ingredients in such a fashion. In fact, one would be motivated to do so since adding the ingredients in slowly gives them ample time to react properly with one another and produce a better yield of product."

The Examiner has further asserted that motivation to meter in partially the 6-APA and/or the phenyglycine derivative is provided because

> "[t]he references clearly wanted to yield the best results possible. To add the reactant in a step wise fashion makes perfect sense since one would want ample time for the reactants to react with one another."

Appellants respectfully disagree for several reasons.

At the outset, it is noted that the disclosure of the secondary reference, WO 420, is only for its disclosure of using D-phenylglycine amide.1/2 H_2SO_4 in water (see, Paper No. 15, page 3, second full paragraph). Therefore, it is evident that the modification of the disclosure of WO '061 to arrive at the subject matters of, for example, independent claims 1 and 17, is not based on the evidence provided by the cited prior art. There is no evidence (and no citations to the record including the disclosures of WO '061 and WO '420) to support the assertion that "[t]o add slowly and in a meticulous manner as in metering is well known in the art and is fully contemplated by the references." Rather, it is respectfully submitted that the alleged "evidence" of motivation to "meter in partially the 6-APA and/or the phenylglycine derivative" is not based on any evidence of record.

As recently explained by the Federal Circuit Court of Appeals, a showing of a suggestion, teaching, or motivation to combine prior teachings "must be clear and particular .... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (1999). The *Dembiczak* decision further explains that,

> "We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, ... (citations omitted) ..., although 'the suggestion more often comes from the teachings of the pertinent references,' (citation omitted). The range of sources available, however, does not diminish the requirement for actual evidence."

In the present case, there is *no actual evidence* to support a finding of motivation to combine the "references." In the case of a single reference (as would be applicable to most of the rejected claims), "there must be a showing of a suggestion or motivation to modify the teaching of that reference." *In re Kotzab*, 208 F.3d 1352, 54 USPQ2d 1308 (Fed. Cir. 2000) ("Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components from combination in the manner claimed."

Moreover, following the "logic" of the assertion that the "best results possible" were no doubt wanted by the inventors of the cited references, it must necessarily be presumed that the inventors disclosed what they believed to be the process yielding the "best results possible." Therefore, that the process, as disclosed, does not describe (or otherwise suggest) the partially metering in or the concentration of the dissolved 6-APA, as claimed here, is itself strong evidence that the inventors of these references did not have in mind Appellant's solution to the problem of providing the best yields or cost savings possible in the enzymatic production of ampicillin.

Considering the primary reference WO '061, the "best results" are directed to overcoming the "potential drawbacks of the known enzymatic methods for production of Ampicillin ...." (See, page 2, lines 18-19). Among these drawbacks the authors mention high costs (yield losses) and investments due to the necessary unit operations incurred when the amino β-lactam is isolated, purified and dried before being used as raw material and "the starting

concentrations of the 6-APA are very low (typically less than 50 mM), thus making the isolation of the formed Ampicillin more difficult and thus more costly." (Page 2, lines 25-28).

Neither the problem to be overcome nor the solution provided in the WO '061 reference, would have led to or suggested the subject matter as set forth in the claims under appeal. One skilled in the art would not, in light of this admonition regarding the drawbacks of the known enzymatic processes, be inclined, for example, to carry out the process while metering in partially the 6-APA and/or the phenylglycine derivative to maintain the concentration of dissolved 6-APA at a relatively low value while also achieving a high total concentration of 6-APA and ampicillin.

Moreover, it is respectfully submitted that the Examiner is improperly attempting to introduce limitations into the claims which are not required by the claim language or intent. The claims do not address the rate of addition, for example, "slowly" or "meticulous." Thus, it is within the scope of the claims to add, including rapidly, all of the 6-APA or the phenylglycine derivative at the beginning of the process to the reaction mixture, as long as the fed (or metered) amount added does not cause, for example, the concentration of dissolved 6-APA, or the total concentration in the reaction mixture of 6-APA and ampicillin, to exceed or fall below the desired amounts.

Neither these amounts nor the methods of accomplishing same or the benefits obtained thereby are addressed in the cited references.

The suggestion of what the artisan would have realized with regard to the manner of adding the reactants, is mere speculation without basis in fact found in the references' disclosures.

Nor is there any objective basis for the assertion that giving the reactants ample time to react with one another would yield the best possible results, or that the time for reaction or manner of charging the reactants to the reaction mixture bears any relationship to the objectives and "solutions" of the references: *e.g.*, for WO '061, to lower costs and increase yield of β-lactam by carrying out the reaction at high concentration of the acylating agent, *see*, page 3, lines

23-25; and for WO '420, to lower effective costs by recovering at least 85% of the phenylglycine amide in pure form, before the β-lactam is separated out, by treating the reaction mixture, after at least the enzyme and solid phenylglycine have been removed with an aldehyde at a pH between 7.5 and 8.5, *see, e.g.,* page 1, line 36 to page 2, line 9. Similarly, there is no disclosed correlation between "giving the reactants ample time to react" and the claim language regarding the concentration of dissolved 6-APA or the other features set forth in the appealed claims or the results obtained thereby.

WO '061 expressly discloses that all of the acylating agent is added to provide a minimum initial concentration in the reaction mixture. However, whether added in portions or all at once, there is no disclosure or suggestion in the art that adding the reactants under conditions which provides a relatively low concentration of dissolved 6-APA (lower than 300 mM), while maintaining at least a minimum total concentration of 6-APA and ampicillin (greater than 250 mM), or which provides a molar ratio of the total quantity of acylating agent to the total quantity of 6-APA would have any effect, much less a beneficial effect, on the outcome of the reaction.

More particularly, the disclosure on page 4, lines 11-19, of WO '061 is that "an important feature" of the invention is that,

> "the concentration of the acylating agent plus the concentration of the β-lactam derivative in the reaction mixture is above 400 mM. One way of obtaining this concentration in the reaction mixture is by adding, in a batchwise process, the acylating agent to the reaction mixture in an amount sufficient to give an initial concentration of the acylating agent in the reaction mixture of more than 400 mM."

Furthermore, on page 5, lines 3-33, of WO '061 it is stated that the process is characterized by the concentration of the starting amino β-lactam in the reaction mixture and, in this respect, the preference is clearly to the higher end of the concentration range. That is,

> "the concentration of the starting amino β-lactam in the reaction mixture is in the range of from about 50 to about 750 mM, preferably above about 100 mM, more preferred above about 150 mM, most preferred above about 200 mM."

Under these conditions, therefore, it is respectfully submitted that the practitioner would not have been motivated to "optimize" the reaction by adding the 6-APA and/or phenylglycine derivative under conditions that would take into consideration the amount of dissolved 6-APA an amount that is not addressed at all in the cited art.

As explained in *In re Freed*, 425 F.2d 785, 165 USPQ 570 (CCPA 1970), a reference that teaches a chemical process would logically and reasonably be inferred as setting out the least number of reactions thought necessary to accomplish the desired objective. Thus, one skilled in the art would logically and reasonably presume that if the reactants were not combined in the manner disclosed in the reference, some adverse side effect or no reaction at all would occur.

Accordingly, in a manner analogous to the number of reaction steps, it is logical and reasonable to assume that the manner of combining the reactants disclosed in WO '061 would necessarily be construed by the practitioner as being required to practice the chemical process there described.

In addition, and as noted above, WO '061 does not describe a solution concentration, i.e., dissolved amount, of 6-APA, lower than 300 mM. Similarly, WO '420, does not describe the dissolved concentration of 6-APA being lower than 300 mM. Accordingly, the combined disclosures of the references must also fail to disclose at least this feature of the present invention.

Similarly, there is no clear disclosure of an enzymatic acylation reaction for ampicillin wherein the molar ratio "k" of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than 2.5, such as less than 2.0.

This molar ratio is not directly disclosed as such in the references. However, according to the examples of WO '061, the lowest value for this ratio k is 2.7. Moreover, the examples also show that when other conditions are the same, the conversion of 6-APA increases at the higher values of k. Insofar as WO '420 uses the same enzymatic coupling reaction as WO '061 (*see, e.g.,* page 3, lines 32-34) and, furthermore, states that the concentration of the reactants is not critical but may be chosen such that upon completion of the enzymatic reaction all

components, except for the D-phenylglycine formed, are still just in solution (*see, e.g.*, page 4, lines 10-13), WO '420 also does not disclose the claimed value of k in the appealed claims. (There is no example in WO '420 of production of ampicillin.)

It is respectfully submitted that the rejection is based upon inappropriate cobbling together of bits and pieces of the prior art using Appellant's disclosure of its own invention as the basis for such reconstruction. "It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the Appellant's structure as a template and selecting elements from references to fill the gaps." *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Therefore, no proper case of *prima facie* obviousness has been established in the record. For this reason alone, the rejection based on the disclosures of WO '061 and WO '420 should not be sustained.

While, for the reasons given above, the claims on appeal are directed to subject matter which would not have been *prima facie* obvious, the rejection should not be sustained for the additional reason that the process as claimed provides unexpectedly superior results which are neither suggested nor obvious over the prior art of record.

The objective of WO '061 is to obtain high conversion with respect to 6-APA. This high conversion is, however, accomplished only at the expense of low conversion of the acylating agent (phenylglycine derivative). Such low conversion is a disadvantage since large amounts of reactants need to be recovered and/or are lost.

Operating under the conditions disclosed in this reference, both high conversion of phenylglycine (PG) derivative and high conversion with respect to 6-APA are not achieved.

More particularly, from those examples in WO '061 which are related to production of ampicillin (as shown in the following table) the conversion with respect to 6-APA varies between 60% and 98% and the conversion with respect to PG derivative varies between 11% and

34%. For the convenience of review, the results of the examples in WO '061 are reproduced below:

Table: examples of WO'61 relating to the preparation of ampicillin (AMP)

Example	Initial conc. 6-APA	Initial conc. PG Deriv.	Ratio k	Total conc. 6-APA+AMP	Conversion of 6-APA	Conversion of PG Deriv.
	mM	MM		mM	(%)	(%)
1 (1st)	100	270	2.7	<100	74	27
1 (2nd)	100	750	7.5	<100	98	13
3 (pH=3)	250	700	2.8	<250	60	21
3 (pH=6.4)	250	700	2.8	<250	94	34
3 (pH=7.0)	250	700	2.8	<250	93	33
4 (T=10 C)	180	700	3.9	<180	95	24
4 (T=20 C)	180	700	3.9	<180	96	25
4 (T=35 C)	180	700	3.9	<180	60	15
5 (1st)	100	270	2.7	<100	74	27
5 (2nd)	100	750	7.5	<100	86	11
6	150	700	4.7	<150	90	19
7	230	920	4	<230	91	23

As shown in the above table, the ratio k is always greater than 2.5, and the total concentration of 6-APA and PG derivative is always less than 250 mM.

For ease of comparison, the following table summarizes results from the specification of the subject application.

Results from Serial No. 09/457,765

	Added 6-APA	Added PG Deriv.	Ratio k	Total conc. 6-APA+AMP	Conversion of 6-APA	Conversion of PG Deriv.
	Mmol	Mmol		mM	(%)	(%)
Example II	600	1000	1.67	>400	96	58
Exp. A	600	950	1.58	>400	92	58

For clarity, it is explained that "conversion" of 6-APA and of PG derivative, is based on the yield of ampicillin (AMP) relative to the total amounts of 6-APA and PG derivative. Thus, in the case of Example II (page 10) the total amount of 6-APA was 600 mmol and the total amount of PGA was 1000 mmol. Therefore, since 575 mmol of AMP was formed the conversions of 6-APA and PGA, are, respectively, (575/600) X 100 and (575/1000) X 100.

It will be recalled that in Experiment A, conditions i) and iii) were both satisfied. A high PG derivative conversion (58%) was achieved, even though condition ii) specifying the low concentration of dissolved 6-APA was not satisfied (during the early part of the experiment the concentration of dissolved 6-APA was higher than 300 mM). This is shown in Graph 2.

When condition ii) (as in Example II) is also satisfied, the conversion for 6-APA increases from 92% to 96% while still maintaining high PG derivative conversion.

These conditions and results are not suggested in the disclosure of WO '061. In fact, considering the results from Example 1 (1^{st}) and Example 1 (2^{nd}) wherein the ratio k increased from 2.7 to 7.5, conversion of 6-APA increased from 74% to 98%. Therefore, one skilled in the art would have expected that at low k values only low 6-APA conversions would be obtained. Similar results are reported in Examples 5 (1^{st}) and (2^{nd}).

As noted from the specification, e.g., page 2, line 23 to page 3, line 2, when working at high total concentration of 6-APA and ampicillin combined and a low molar ratio of the total quantity of added phenylglycine derivative to the total quantity of added 6-APA (below 2.5), the conversions of 6-APA and PG derivative, may be unexpectedly increased. In addition to high

conversions of both 6-APA and PG derivative, stirrability of the reaction may also be improved when condition ii) is satisfied.

Since there is no suggestion in the disclosure of WO '061 to operate at the conditions specified in the present claims and, absent motivation to operate at a k ratio < 2.5, and at a total concentration of 6-APA and ampicillin greater than 250 mM, much less at the totally undisclosed low concentration of dissolved 6-APA (as opposed to undissolved/solid 6-APA), the present invention would not have been obvious over the cited references.

Furthermore, while it has been found that high conversions to β-lactam derivatives, such as cephalexin, are achieved at high concentrations of the reactants, including the β-lactam nucleus, in the preparation of ampicillin by the enzymatic reaction of 6-APA, it was surprisingly found that the presence of a high concentration of 6-APA results in only relatively low conversions to ampicillin (page 2, lines 17-22).

According to embodiments of the present invention this problem is overcome by maintaining the concentration of dissolved 6-APA in the reaction mixture, at relatively low concentration, whereby the conversion of 6-APA to ampicillin is higher than would be achieved by operating at a higher concentration of the dissolved 6-APA (page 2, lines 23-28). Embodiments of the invention provide the further advantage that at the relatively low concentration of dissolved 6-APA, the stirrability of the reaction mixture is improved (page 2, line 29 to page 3, line 2).

The Examiner has stated that it is not clear where these results have come from nor that they are based in fact, and that Appellant must present the results in a declaration by the inventors.

It is respectfully submitted that there is no such requirement and that the evidence provided by the examples reported in the specification should be taken into consideration in reaching the final determination of obviousness. See, for example, *In re Margolis,* 75 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986). It is respectfully submitted that the examples of the cited prior

art references provide evidence of the reasonable expectation of the practitioner of ordinary skill in the art with regard to the teachings of that reference.

Accordingly, it is submitted that it is reversible error for the Examiner to have failed to consider the comparisons based on the examples taken from the disclosure of WO '061 and the examples from the specification of the subject application, which comparisons support the conclusion that the process as disclosed and claimed herein, provides unobvious and unexpected results.

Therefore, for any and all of the reasons set forth herein, the rejection of claims 1-4, 6, 7 and 14-17 under 35 U.S.C. § 103(a) as being unpatentable over WO 92/01061 (WO '061) taken with WO 95/03420 (WO '420), should also not be sustained, and should be reversed by the Honorable Board of Patent Appeals and Interferences.

Respectfully submitted,

MAYER BROWN ROWE & MAW

By: _____ Reg. No. 36,004
Richard A. Steinberg
Registration No. 26,588
Direct No. (202) 263-3325

Mayer, Brown, Rowe & Maw LLP
Intellectual Property Group
1909 K Street
Washington, D.C. 20006-1101
Customer No.: 000043569

(viii) CLAIMS APPENDIX

1. A batch process for preparation of ampicillin comprising:

acylating 6-aminopenicillanic acid (6-APA) with a phenylglycine derivative in the presence of and an enzyme to form a reaction mixture wherein the process is carried out while

i) maintaining the total concentration in the reaction mixture of 6-APA and ampicillin combined is substantially throughout the reaction, greater than 250 mM;

ii) metering in partially the 6-APA and/or the phenylglycine derivative in the course of the acylation reaction to thereby maintain the concentration of dissolved 6-APA is lower than 300 mM throughout the reaction; and

iii) maintaining the molar ratio of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than 2.5.

2. Process according to Claim 1, wherein the acylation reaction is carried out while the total concentration of the 6-APA and ampicillin present in the reaction mixture is, substantially throughout the reaction, greater than 300 mM.

3. Process according to any one of Claims 1 or 2, wherein the acylation reaction is carried out while metering in partially the 6-APA and/or the phenylglycine derivative to thereby maintain the concentration of dissolved 6-APA is kept lower than 250 mM throughout the reaction.

4. Process according to claim 1, wherein the acylation reaction is carried out while the molar ratio of the total quantity of phenylglycine derivative to the total quantity of 6-APA is less than 2.0.

6. Process according to Claim 1, wherein the phenylglycine derivative is metered in as a salt of D-phenylglycine amide and an acid.

7. Process according to Claim 6, wherein the phenylglycine derivative is metered in the form of a solution of D-phenylglycine amide.1/2 H_2SO_4 in water.

14. Process according to Claim 1, which comprises charging wherein, in order to maintain the concentration of dissolved 6-APA lower than 300 mM throughout the reaction, a portion of the total amount of 6-APA is charged to the reaction mixture at the beginning of the reaction such portion providing a concentration of dissolved 6-APA less than 300 mM and introducing the remainder of the total amount is introduced during the remainder of the acylation reaction to maintain the concentration of dissolved 6-APA less than 300 mM.

15. Process according to Claim 14, wherein the concentration of dissolved 6-APA is kept lower than 250 mM throughout the acylation reaction.

16. Process according to Claim 15, wherein the total concentration of the 6-APA and ampicillin present in the reaction mixture is, substantially throughout the acylation reaction, greater than 300 mM.

17. A process for the preparation of ampicillin by acylating a quantity of 6-aminopenicillanic acid (6-APA) with a quantity of phenylglycine derivative and an enzyme in an aqueous reaction medium to provide a reaction mixture containing dissolved 6-APA; said process comprising

initially introducing a part of said quantity of the 6-APA and/or a part of the quantity of phenylglycine derivative into the reaction medium under conditions allowing ampicillin to be formed by the acylation reaction and,

thereafter adding the rest of the quantity of 6-APA and/or phenylglycine derivative, under conditions whereby ampicillin will continue to be formed by the acylation reaction, and

wherein the concentration of dissolved 6-APA in the reaction mixture is, throughout the acylation reaction, lower than 300 mM and the total combined concentrations in the reaction mixture of 6-APA and formed ampicillin is greater than 250 mM; and further

wherein the molar ratio of the quantity of phenylgylcine derivative to the quantity of 6-APA is less than 2.5.

(ix) Evidence Appendix

None.

(x) Related Proceedings Appendix

None.

APPENDIX FOR RULES & STATUTES

APPENDIX FOR CASES